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EXAMINER

MARVICH, MARIA

ART UNIT PAPER NUMBER

1633

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/909,460

Applicant(s)

LUNS福德 ET AL.

Examiner

Maria B. Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7-22, 24, 26, 27, 29-36, 51-58 and 62-84 is/are pending in the application.
- 4a) Of the above claim(s) 17, 22, 24, 27 and 29-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-21, 26, 33-36 and 51-84 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

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DETAILED ACTION

Claims 1-5, 7-22, 24, 26, 27, 29-36, 51-58 and 62-84 are pending. Claims 17, 22, 24, 27 and 29-32 have been withdrawn. Therefore, claims 1-5, 7-17, 18-21, 26, 33-36 and 51-84 are pending in the application.

Claim Objections

Claims, 8, 14, 16 and 51 are objected to because of the following informalities: Claim 14 recites "consisting of at least" in line 2. however, use of the closed term "consisting of" with "at least" which implies open language of comprising more than certain elements and amounts is not consistent. Either the claim should be amended to delete "at least" or to substitute "consisting of" with --comprising--.

When referring to previously recited limitations it is customary to reference these limitations using either --the-- or --said--. In claim 16, "a peptide" should be amended to --the peptide--. In claim 51, "a target site" and "a mammal" should similarly be amended for clarity of antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 1-4, 7-10, 18, 33, 34, 52-55, 62, 65-67, 70, 71, 74-76 and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lambert et al (Biochimie, 1998, Vol 80, pages 969-976; see entire document) or Balland et al (NATO ASI Series, 1996, Vol 290, pages 131-142; see entire document) in view of Knepp et al (US 6,264,990; see entire document).

The instant claims are drawn to a microparticle less than 20 microns in diameter comprising a polymeric matrix, a lipid and a nucleic acid further comprising a carbohydrate.

Lambert et al teach a microparticle less than 20 microns in diameter (see e.g. page 972, col 2, paragraph 2) comprising a polymeric matrix, a lipid and a nucleic acid (see e.g. page 970, col 1, paragraph 4- col 2, paragraph 3) and preparations of these microparticles (see e.g. table 1) as recited in claims 1, 7 and 52. Lambert et al teach antisense oligonucleotides associated with nanoparticles and the cationic lipid cetyltrimethylammonium (CTAB), (see e.g. page 970, col 2, paragraph 3) as recited in claims 53-55. The particles are resuspended in medium (see table 1), which is a pharmaceutically acceptable carrier as recited in claim 70. The nucleic acid is an oligonucleotide as recited in claim 75. The polymeric matrix is polyisobutylcyanoacrylate (see e.g. bridging paragraph col 1-2, page 970), which is a synthetic biodegradable copolymer as evidenced by Balland et al (see e.g. page 131, paragraph 1) as recited in claims 65 and 66.

Balland et al teach a microparticle less than 20 microns in diameter (see e.g. page 132, paragraph 4) comprising a polymeric matrix, a lipid and a nucleic acid (see e.g. page 132, paragraph 4- 5) and preparations of these microparticles (see e.g. page 133, paragraph 4) as recited in claims 1, 7 and 52. The lipid is cetyltrimethylammonium (CTAB) and is cationic (see e.g. page 131, paragraph 2) as recited in claims 53-55. The particles are resuspended in PBS (see page 133, paragraph 4), which can be a pharmaceutically acceptable carrier as recited in claim

70. The nucleic acid is an oligonucleotide as recited in claim 75. The polymeric matrix is polyisohexylcyanoacrylate (PIHCA), which is a synthetic biodegradable copolymer (see e.g. page 131, paragraph 1 and page 132, paragraph 4) as recited in claims 65 and 66. Balland et al teach that the nucleic acid was protected against enzymatic degradation (see table 1) and uptake by cells was dramatically increased (figure 2) by complex formation with CTAB.

Neither Lambert et al nor Balland et al teach a composition, in particular that a microparticle further comprises a carbohydrate.

Knepp et al teach formation of a nucleic acid particle comprising lipids, nucleic acids and carbohydrates such as sucrose that function as protecting agents (see e.g. col 8, line 14-22 and col 10, line 27-36). Knepp et al teach that lipid nucleic acid complexes facilitate nucleic acid uptake into cells *in vitro* and *in vivo* (see e.g. bridging paragraph, col 5-6). The nucleic acids are circular and include oligonucleotides, plasmids and expression constructs (see e.g. col 7, line 54 and col 15, line 49) and peptides that lead to immunogenic responses such as against a pathogenic organism (see e.g. col 9, line 17-22). As well, Knepp et al teaches that the nucleic acid can be part of a PLGA particle (see e.g. col 9, line 44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the carbohydrate such as sucrose as taught by Knepp et al in the microparticles taught by Lambert et al or Balland et al because Knepp et al teach that it is within the ordinary skill of the art to use carbohydrates in a nucleic acid delivery particle comprising lipids and nucleic acid and because Balland et al and Lambert et al teach that it is within the ordinary skill of the art to deliver nucleic acids as part of microparticles that comprise polymeric matrices and lipids. One would have been motivated to add carbohydrate to the microparticles

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for their protective properties. Knepp et al demonstrates an attempt to use known techniques to improve similar microparticles as Balland et al and Lambert et al using skill that was available at the time of filing with well-established methods on well-characterized systems. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-5, 7-9, 11, 13, 16, 18, 21, 26, 33, 34, 51-54, 56, 58, 62, 64, 65, 70-76 and 81-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Knepp et al (US 6,264,990; see entire document).

Papahadjopolous et al teach a lipidic microparticle comprising lipids and nucleic acids (see e.g. abstract) and polymeric matrices (see e.g. col 3, line 50-67). The invention is designed to provide lipid: nucleic acid complexes that have increased shelf life, for transfection of mammalian cells *in vitro* or *in vivo* or *ex vivo* (see e.g. col 18, line 50-53). The lipidic-microparticles can be made with amphiphilic cationic lipids complexed with nucleic acids and polymer (see e.g. col 7, line 16-29). The microparticles can be part of a preparation and are each less than 11 microns (see e.g. col 8, line 34-41 and col 18, line 29-47) as recited in claims 1, 7, 52 and 64. The nucleic acid can be part of an expression cassette that is disclosed as being expression vectors or plasmids, which are circular, expressing polypeptides (see e.g. col 8, line 21-26, col 11, line 41-51) as recited in claim 2-4, 62 and 71. The lipids of the microparticle can be amphiphilic cationic lipids such as phospholipids (see e.g. col 6, line 41-51) and the microparticles and hence the preparations of microparticles are also associated with a second

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lipid or neutral helper lipid (see e.g. col 3, line 31-50) as recited in claim 9, 11, 13, 53, 54, 56 and 58. The expression cassettes encode polypeptides such as globin, which comprise at least 7 amino acids identical to at least a fragment of a naturally occurring mammalian protein as recited in claim 8 and 16. The microparticles further comprise a targeting moiety (see e.g. abstract) as recited in claim 5. The targeting moiety can be attached to the microparticle during production or can be expressed by the nucleic acid of the microparticle. The targeting moieties are immunogenic peptides as recited in claims 18 and 21 such as ligands, growth factors or cytokines (see e.g. col 7, line 4-16, col 15, line 31-52) and Paphadjopolous specifically describes targeting moieties that recognize MHC complexes (i.e. MHC I) (see e.g. col 15, line 23-col 16, line 11), peptides that bind MHC molecules as recited in claim 8 (b). The instant specification describes proteinaceous antigenic determinants as containing an epitope, which limitation is met by the use of ligands on the microparticle. Thus a microparticle with such a targeting moiety and a nucleic acid encoding an antigenic polypeptide such as hGH (see e.g. col 19, line 32-37) meets the claim limitations as recited in claim 72 and 73. Paphadjopolous further contemplate administration of the microparticles to mammals for gene therapy in which the microparticle is administered in an effective amount at a target sites such as the circulatory system (see e.g. col 4, line 51-66 and col 8, line 8, line 64-67) as recited in claim 51. Specifically, Paphadjopolous describe targeting the microparticles to immune cells (see e.g. col 22, line 46-64), which would result in elicitation of an immune response as recited in claim 34. Furthermore, it is contemplated that the microparticle encode a trafficking signal (see e.g. col 12, line 4-12) as recited in claim 26 or an oligonucleotide (see e.g. col 19, line 10-31) as recited in claim 74, 75 and 76. The microparticle can be a preparation of particles and is in a pharmaceutically acceptable carrier (see e.g. col

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8, line 34-41) as recited in claim 33 and 70. The polymer can be spermine, a biodegradable polymer (see e.g. col 3, line 50-52) as recited in claim 65.

Paphadjopolous do not teach inclusion of a carbohydrate i.e. sucrose in the particle.

The teachings of Knepp et al are reviewed above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the carbohydrate or sucrose as taught by Knepp et al in the microparticles taught by Paphadjopolous because Knepp et al teach that it is within the ordinary skill of the art to use carbohydrates in a nucleic acid delivery particle comprising lipids and nucleic acid and because Paphadjopolous teaches that it is within the ordinary skill of the art to deliver nucleic acids as part of microparticles that comprise polymeric matrices and lipids. One would have been motivated to add carbohydrate to the microparticles for their protective properties. Knepp et al demonstrates an attempt to use known techniques to improve similar microparticles as Paphadjopolous using skill that was available at the time of filing with well-established methods on well-characterized systems. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 12, 57 and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Knepp et al (US 6,264,990; see entire document) as applied to claims 1-5, 7-9, 11, 13, 16, 18, 21, 26, 33, 34, 51-54, 56, 58, 62, 64, 65, 70-76 and 81-84 above, and further in view of Debs et al (US 5,827,703; see entire

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document). Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The lipid is phosphatidylcholine or phosphatidylethanolamine.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous teaches that the lipids are phospholipids but does not teach that these phospholipids are specifically phosphatidylcholine or phosphatidylethanolamine.

Debs et al teach methods for introducing genes into cells by complexing DNA to lipid carriers (see e.g. abstract). The lipidic carriers are preferably phosphatidylcholine and phosphatidylethanolamine as these are suitable compounds for repeated injection into mammalian hosts.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use phosphatidylcholine or phosphatidylethanolamine as taught by Debs et al in the lipid microparticles taught by Paphadjopolous et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles using phospholipids to generate lipid:nucleic acid complexes and because Debs et al teach that it is within the ordinary skill of the art to use phosphatidylcholine and phosphatidylethanolamine to form lipid:nucleic acid complexes for gene delivery. One would have been motivated to do so in order to receive the expected benefit of forming particles with phosphatidylcholine or phosphatidylethanolamine that is suitable for repeated administration in mammals. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

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Claims 14, 15, 19, 20 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Knepp et al (US 6,264,990; see entire document) as applied to claim 8 above, and further in view of Fikes et al (US 6,534,482; see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The microparticles are designed to deliver arrayed peptides.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the microparticles are designed to deliver arrayed peptides.

Fikes et al teach development of nucleic acid vaccines comprising multiple MHC I and II epitopes employing a peptide or arrays of peptides for use as an immunogenic composition (see e.g. abstract). One or more MHC I epitopes (CTL epitopes) are fused together (see e.g. col 5, line 18-31). The peptides are synthesized with overlapping sequences that are then shared to form a multiepitope compound in which the peptides are then arranged in tandem (see e.g. col 21, line 17-30). The epitopes are contained on an expression vector (see e.g. col 20, line 32-45) and introduced into mammals to elicit immune responses following delivery to the mucosal tissue such as vaginal tissue (see e.g. bridging paragraph col 23-24). The DNA is delivered for therapeutic purposes (see e.g. col 24, line 30-37).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the lipid microparticles taught by Paphadjopolous et al to deliver the nucleic acid encoding immunogenic peptides such as those that bind to MHC I molecules as taught by Fikes et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to

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generate lipid microparticles, comprising nucleic acid encoding therapeutic compositions, for delivery to mammals and because Fikes et al teach that it is within the ordinary skill of the art to employ arrays of peptides in a plasmid expression vector for therapeutic purposes such as to elicit an immune response. One would have been motivated to do so in order to receive the expected benefit of using microparticles designed to provide lipid:nucleic acid complexes that have increased shelf life, for transfection of mammalian cells *in vitro* or *in vivo* or *ex vivo* (see Paphadjopolous et al, col 18, line 50-53) to deliver the immunogenic compositions that are effective in eliciting immune responses (see Fikes et al, col 24, line 30-37). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Knepp et al (US 6,264,990; see entire document) as applied to claim 52 further in view of Hedley et al (US 5,783,567; see entire document) or Ando et al (J Pharmaceutical Sciences, 1999, pages 126-130; see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The microparticles comprises nucleic acids of which at least 50% are supercoiled.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the microparticles comprises nucleic acids of which at least 50% are supercoiled.

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Hedley et al teach a preparation of microparticles made up of a polymeric matrix and nucleic acids of which at least 50% are supercoiled (see e.g. abstract). The nucleic acid is supercoiled for more efficient transfection. Means are taught to protect the integrity of the nucleic acid such as minimizing shearing forces and limiting sonication (see e.g. col 8, line 2-12)

Ando et al teach use of supercoiled DNA that is 85% supercoiled as supercoiling of the DNA is essential for its bioactivity (see e.g. page 126, col 2, paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that at least 50% of the nucleic acid molecules in the microparticles taught by Paphadjopolous et al are supercoiled as taught by Hedley et al and Ando et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles for gene delivery complexed to microparticles and because Hedley et al and Ando et al teach that it is within the ordinary skill of the art to preserve the integrity of nucleic acid supercoiling. One would have been motivated to do so in order to receive the expected benefit of microparticles designed to improve transfection efficiency and bioactivity. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 66-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Knepp et al (US 6,264,990; see entire document) as applied to claim 52 further in view of Cleek et al (J Biomedical

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Materials Res, 1997, pages 525-530; see entire document) as evidenced by Manoharan et al (2005/0153337; see entire document).

Applicants claim a preparation comprising a plurality of microparticle each of which comprises lipids, nucleic acids and polymeric matrices. The polymeric matrix is PLGA wherein the ratio of lactic acid to glycolic acid is in a range of 1:2 to about 4:1 or about 65:35 by weight.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the polymeric matrix is PLGA wherein the ratio of lactic acid to glycolic acid is in a range of 1:2 to about 4:1 or about 65:35 by weight.

Cleek et al teach use of microparticles for inhibition of smooth muscle cell growth. The microparticles are comprised of nucleic acid and PLGA, one of the few synthetic biodegradable polymers approved for human clinical use (see e.g. page 525, col 2, paragraph 2). PLGA degradation *in vivo* occurs by random non-enzymatic hydrolysis of the polyester bonds along the polymeric backbone at a rate dependent on the copolymer ratio. As they are hydrolyzed to lactic acid and glycolic acid, they are processed normally by the metabolic pathway and eliminated as carbon dioxide (see e.g. page 525, col 2, paragraph 2). The biodegradable PLGA particles were formed in a 1:1 ratio which is in the range of 1:2 to 4:1 and is about 65:35 ratio given that the term "about" is a relative term for which the specification provides no definition. The PLGA served as effective delivery agents (see e.g. page 529, col 2, paragraph 4). While Cleek et al do not teach that the ratio of lactic acid to glycolic acid is "by weight", classically synthesis of PLGA from lactic acid and glycolic acid involves a combination of the monomers "by weight" as evidenced by Manoharan et al (see e.g. paragraph 0873).

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PLGA particles as taught by Cleek et al in the lipid microparticles taught by Paphadjopolous et al because Cleek et al teach that it is within the ordinary skill in the art to use PLGA to deliver nucleic acids to cells and because Paphadjopolous et al teach that it is within the ordinary skill of the art to complex synthetic polymers, i.e. PLGA, to nucleic acid for stable delivery to cells. One would have been motivated to do so in order to receive the expected benefit that the microparticles comprised of PLGA are among the few synthetic biodegradable polymers approved for human clinical use because they are hydrolyzed to lactic acid and glycolic acid, they are processed normally by the metabolic pathway and eliminated as carbon dioxide and they serve as effective delivery agents (see Cleek et al, page 525, col 2, paragraph 2 and page 529, col 2, paragraph 4). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Based upon a reconsideration of the art, the previous new rejections have been made.


Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Maria B Marvich, PhD
Examiner
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